REMARKS

After amendment of claim 21, claims 1-21, 23, and 34-37 will be pending in this application, with claims 1-20 withdrawn from consideration and claims 22 -33 canceled. Claims 21 and 34-37 are currently under examination.

Former claims 21, 23, and 34-37 were rejected under 35 USC 112, ¶1. Former claims 21 and 34-36 were rejected under 35 USC § 102(b) over Meyers et al. (US 2002/0009779). Former claims 21 and 34-36 were rejected under 35 USC § 103(a) over Meyers et al. (US 2002/0009779) in view of Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866). The rejections under 35 USC § 102(b) and 35 USC § 103(a) are respectfully traversed.

The Office Action has asked that the sequences in the application be identified and that sequence listings be prepared pursuant to 37 CFR §§1.821-1.825. Applicants submit that these requirements were met in the preliminary amendment received by the patent office on 7 January 2005 (certificate of mailing date of 4 January 2005). Applicants do not believe that any further submission of sequence listings or amendments to the specification to identify sequences are necessary.

The Amendment

Entry of the present amendment to the claims is respectfully requested. No new matter is added by the amendment, because the amended claims find full support in the application as filed.

Claim 21 steps (iv) and (vi) have been amended to replace the term "an agent" with "the agent. Claim 21 has also been amended to incorporate the limitations of claim 23.

The 35 USC § 112, ¶1 rejection

Former claims 21, 23, and 34-37 have been rejected under 35 USC 112, ¶1 for being indefinite. Claims 23 and 34-37 are dependent directly or indirectly from claim 21. Claim 21 steps (iv) and (vi) have now been amended to introduce the proper antecedent basis with respect to the term agent. Withdrawal of the rejection of these claims under 35 USC 112, ¶1 is respectfully requested.

The 35 USC § 102(b) rejection

Former claims 21 and 34-36 were rejected as being unpatentable over Meyers et al. (US 2002/0009779). This rejection is respectfully traversed. However in the interest of expediting

prosecution of this application, the limitation of now canceled claim 23 has been incorporated into claim 21. The Office Action has acknowledged in the discussion of the 35 USC § 103(a) rejection that the step of determining the level of glucose induced insulin in former claim 23 is not taught in Meyers et al.. Withdrawal of the rejection under 35 USC § 102(b) is respectfully requested.

The 35 USC § 103(a) rejection

Former claims 21 and 34-37 were rejected as being unpatentable over Meyers et al. (US 2002/0009779) in view of Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866). This rejection is respectfully traversed, as the teachings of Meyers et al. and Ling et al. do not support a rejection of *prima facie* obviousness.

Claims 21 and 34-37 as amended are directed to methods for identifying an agent for treating a diabetic or pre-diabetic individual, comprising steps including *in vitro* and *in vivo* testing of the agent. Step (v) recites determining the level of insulin secretion in response to glucose.

The Supreme Court in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) recently affirmed the factual analysis set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966) Id. at 1734. Known as the "Graham factors", the appropriate obviousness analysis requires an inquiry into: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims at issue; and 3) the level of ordinary skill in the art. The court further affirmed that considerations of any teachings, suggestions, or motivations for combining previous known elements and whether or not such combinations would have led to predictable results can form an important part of the analysis.

Meyers et al. and Liang et al. do not teach that an agent capable of inhibiting the hexokinase V (SEQ ID NO:2) of claim 21 would be useful in treating or preventing diabetes and that such an agent can be selected by observing the level of insulin secretion in response to glucose in animals treated with this agent.

Meyers et al. teaches (paragraphs **[0001]** to **[0003]**) that there are four separate types of hexokinases, with hexokinase IV being known as glucokinase. Collectively, the hexokinases can be found in virtually all cells as they are essential in processing sugars for cellular energy, with glucokinase (hexokinase IV) being found only in liver and pancreatic β-cells.

Meyers et al. further teaches that they have identified a new hexokinase which they refer to as 50365; the Office action states that the 50365 sequence disclosed by Meyers et al. "is identical to the instantly claimed polypeptide of SEQ ID NO. 2." Meyers in paragraph **[0440]** teaches the tissue distribution of 50365 mRNA where Meyers tested "human tissues and several cell lines". However, this tissue distribution is the only evidence offered by Meyers et al. with respect to the properties of 50365. Examples 1-3 of Meyers et al. shows that 50365 mRNA was found to be upregulated in certain cancer cells as compared to normal cells, including colon, liver, breast, ovary, cervix, and lung as well as HMVEC (human microvascular endothelial cells), pooled hemangiomas, and HCT (colorectal carcinoma) cell types. Noticeably absent is any evidence that hexokinase V is found in the pancreas, the organ containing the β cells from which insulin, a hormone that plays a central role in diabetic disorders, is produced. Only the present application provides a teaching that hexokinase V is expressed in the β islet cells of the pancreas and that hexokinase V is overexpressed in the islet cells of diabetic mice (see Example 2).

The disclosure of Meyers et al. therefore teaches away from the claimed method of identifying an inhibitor for treating or preventing diabetes in favor of treating a proliferative disease. As hexokinases are enzymes that phosphorylate sugars as part of the glycolytic pathway that generates cellular energy in the form of ATP, it is reasonable to expect that the proliferative nature of cancer cells requires an upregulation of hexokinases that can process sugars necessary for growth and division, and that an impairment of this ability would have therapeutic utility.

Importantly, Meyers et al. does not provide any information on the biological *role* of 50365 in any metabolic disorder and consequently cannot provide any teachings as to the desirability of inhibiting 50365 for preventing or treating these disorders. It is important to note that not all hexokinases have similar biological properties. Figure 2 of the present application shows a comparison of hexokinase V with hexokinases I-IV. It is clear from the figure that hexokinase V is more similar to hexokinase I-II than it is to glucokinase (hexokinase IV). In fact, in the present application, Example 1 confirms that the amino acid sequence identities of hexokinase V as compared to I-IV are respectively 71%, 68%, 54%, and 53%. Thus hexokinase V is least similar to hexokinase IV with a sequence identity of only 53%. Example 2 also teaches that the enzyme affinity of hexokinase V for glucose is least similar to hexokinase IV.

The Km (binding affinity to glucose) of hexokinases I-II are in the range of 0.1-0.2 mM while the Km of glucokinase (hexokinase IV) is 8 mM. Hexokinase V was found to be most similar to hexokinases I-II with a Km of 0.15 mM.

But the state of the art is deficient in supporting the notion that inhibition of hexokinases most similar to hexokinase V (e.g. hexokinases that are not hexokinase IV) can be effective in treating or preventing a metabolic disorder like diabetes, or that one would select such an inhibitor by determining its ability to affect the level of glucose-induced insulin secretion as described in the pending claims. Liang et al. teaches that while hexokinases are known to be enzymes that mediate the important metabolic processes of processing sugars for energy in virtually all cells, it is glucokinase (hexokinase IV) that has an *additional* function of sensing increased glucose concentration and subsequently mediating increased insulin secretion. Specifically Liang teaches that as glucose concentrations increase in the culture medium of the pancreatic β cells, so too does glucokinase (hexokinase IV) activity and insulin secretion. In contrast, hexokinase activity (the hexokinase type(s) was unspecified by Liang et al. but was one that was not glucokinase) did not parallel the change in insulin secretion (the values of hexokinase activity at the three different glucose concentrations tested were all within the experimental error range of each other). Thus Liang et al. teaches that only gluokinase (hexokinase IV) mediates glucose induced insulin secretion and that other hexokinases do not. Consequently Liang et al. does not teach inhibiting a hexokinase that is similar to hexokinases I-III to prevent or treat diabetes. Liang et al. also teaches away from monitoring the levels of glucose induced insulin secretion to select an inhibitor of a hexokinase similar to hexokinases I-III, as the level of insulin secretion in response to glucose does not correlate with the activity of these types of hexokinases.

The state of the art therefore teaches that of the hexokinases I-IV, the 50365 protein of Meyers et al. is most dissimilar to hexokinase IV when tissue localization, sequence identity, and glucose binding affinity are considered, and that only hexokinase IV is regulated by glucose for glucose induced insulin secretion. The present application however teaches that the insulin producing islet cells of diabetic mice over-express hexokinase V and that there is an unexpected link between hexokinase V expression and glucose induced insulin secretion. In particular, Figure 10 of the present application shows the release of insulin as a function of glucose

concentration. In the control cells over-expressing a control protein (GFP, green fluorescent protein was chosen because it is not coupled to the insulin secretion pathway), insulin release increases as expected with increasing glucose concentrations of 2mM, 5mM, and 16mM. Surprisingly, cells over expressing hexokinase V show comparably lower insulin release at the higher 16mM glucose concentration. This unexpected finding suggests that over-expressed hexokinase V is disrupting the sensitivity of insulin response to glucose through some unknown mechanism; i.e. over-expression of hexokinase V is detrimental to glucose induced insulin secretion. These experiments and results are neither suggested nor expected based on the teachings of Meyers et al. or Liang et al., either alone or in combination. Thus only the teachings of the present application would motivate one of skill in the art to search for inhibitors of hexokinase V for treating or preventing diabetes by identifying inhibitors of hexokinase V according to the steps of the pending claims and in particular according to the step of determining the insulin secretion response to glucose of animals treated with the inhibitor.

For the reasons stated, withdrawal of the rejection of amended claims 21 and claims 34-37 is respectfully requested.

Applicants respectfully submit that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested. If the Examiner believes a telephone conversation would help advance prosecution of the present application, the Examiner is cordially invited to contact the undersigned at the number below.

Respectfully submitted,

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